REMARKS

Applicants would like to thank Examiner James Schultz for his time and helpful suggestions during his interview with one of the applicants, Dr. James Donegan and the undersigned, Applicants' representative on June 29, 2006. During the interview, Applicants discussed the rejections in the instant Office Action and proposed claim language. Specific issues raised in the interview will be addressed in the body of the response.

Claims 245, 248-251, 253-255, 260, 264, 265, 268, 270, 272, 284, 288-290, 296, 299, 303, 304, 308-313 and 317 are currently being considered in the above-referenced application. Claim 317 has been canceled without prejudice. As will be discussed in below, claims 245, 265, 272, 299 and 308-311 have been amended to more distinctly claim that which Applicants regard as their invention. These amendments are supported by the specification.

As will also be discussed in further detail below, claim 324 has been added. It is supported by the specification.

1. The Rejections Under 35 USC §112, Second Paragraph

Claims 272, 253, 254, 308, 317 and 272 have been rejected under 35 USC §112, second paragraph. Each of these rejections will be addressed below.

1.1 Claim 272

The Office Action specifically states with respect to claim 272:

> Claim 272 was previously rejected, because said claim recites the composition of claim 265 that is single-stranded. However claim 265 requires at least two stem loops in the structure. Because stem loop structures are necessarily double stranded, the requirement of claim 272 for single-strandedness is not considered capable of being met.
>
> Applicants have traversed the instant rejection by asserting that "'single-stranded' only refers to a single strand, and also includes a single-stranded nucleic acid having some double stranded character when there is some self hybridization within the single strand".

> This argument is not considered convincing, since applicants assertion that a sequence that has some double stranded character may still be considered a single-stranded sequence runs contrary to the accepted definition of the prior art. Since applicants do not appear to have provided a more specific definition, which explicitly states that a single-stranded molecule may contain some double stranded character while still being considered a single-stranded molecule, it is maintained that the plain meaning of "single-stranded" is that which is not double stranded.

Applicants respectfully traverse the rejection. This rejection was discussed during the June 29, 2006 interview. As discussed during the interview, Applicants note that the assertion that "'single-stranded' only refers to a single strand, and also includes a single-stranded nucleic acid having some double stranded character when there is some self hybridization within the single strand" is not an "argument" but a point of information. As discussed, it is Applicants view that it is well accepted among those of ordinary skill in the art that "single stranded" sequences may also include intrastrand base pairing. A "single stranded" sequence where intrastrand base pairing takes place is merely considered to contain different secondary structure. For Examiner's reference, Applicants submit hereto as Exhibits 1 and 2 copies of references published on or before the priority date of the above-referenced application where clearly single stranded sequences containing regions of intrastrand base pairing are still considered to be single-stranded.

In view of the above arguments, Applicants assert that the rejection of claim 272 under 35 USC §112, second paragraph has been overcome. Therefore, Applicants respectfully request that the rejection be withdrawn.

1.2 Claims 253 and 254

It is asserted with respect to claims 253 and 254:

> Claims 253 and 254 recite the limitation "said signal processing sequence" in claim 245. There is insufficient antecedent basis for the term "processing" in these claims.

In response and as discussed during the interview on June 29, 2006, claim 245 has been amended to recite that the composition further comprises a "signal

processing sequence". Thus there is now sufficient antecedent basis for the term "processing".

In view of the amendment of claim 245, Applicants assert that the rejection of claims 253 and 254 under 35 USC §112, second paragraph has been overcome. Therefore, Applicants respectfully request that the rejection be withdrawn.

1.3 Claim 308

It is asserted with respect to claim 308 that:

> Claim 308 recites the limitation "said complementary specific nucleic acid sequence" in claim 299. There is insufficient antecedent basis for this limitation in the claim.

In response and as discussed during the interview on June 29, 2006, claim 308 has been amended to recite that the specific nucleic acid sequence is "complementary with a specific portion of viral or cellular RNAs" produced act as antisense. In view of the amendment of claim 308, Applicants assert that the rejection of claim 308 under 35 USC §112, second paragraph has been overcome. Therefore, Applicants respectfully request that the rejection be withdrawn.

1.4 Claim 317

The Office Action specifically states with respect to claim 317:

> Claim 317 recites the limitation "said tertiary nucleic acid is RNA" in claim 245. There recites the limitation "gene product" in claim 265. There is insufficient antecedent basis for this limitation in the claim.

Applicants respectfully traverse the rejection. However, in order to advance prosecution and as discussed during the interview on June 29, 2006, claim 317 has been canceled. Applicants do reserve the right to file subsequent continuation and/or divisional applications claiming the canceled subject matter. Therefore, the rejection of claim 317 under 35 USC §112, second paragraph has been overcome and should be withdrawn.

1.5 Claim 272

The Office Action specifically states with respect to claim 272:

> Claim 272 recites the limitation "gene product" in claim 265. There is insufficient antecedent basis for this limitation in the claim.

In response and as discussed during the interview on June 29, 2006, claim 272 has been amended to recite that that the "nucleic acid synthesized by said nucleic acid construct" is single-stranded. In view of the amendment of claim 272, the rejection of claim 272 under 35 USC §112, second paragraph has been overcome. Therefore, Applicants respectfully request that the rejection under 35 USC §112, second paragraph of claim 272 be withdrawn.

2. The Rejections Under 35 USC §101

Claims 245, 248, 249, and 251, 253-255, 260, 264, 299, 303, 304, 308-313 and 317 have been rejected under 35 U.S.C. §101. The Office Action specifically states:

> The rejection of claims 245, 248, 249, and 251, 253-255, 260, and 264, are based upon the breadth of the claim language, which previously read: "a composition comprising a primary nucleic acid component, which upon introduction into eukaryotic cell synthesizes a secondary nucleic acid which synthesizes a gene product, or a tertiary nucleic acid, or both, in said eukaryotic cell, wherein said primary nucleic acid is not obtained with said secondary or tertiary nucleic acid or said gene product". Such language was considered to read on non-statutory subject matter, because a human is considered to be a composition comprising a primary nucleic acid that has the claim limitations. The claims as cited above were also considered to read on nonstatutory subject matter as reading on products of nature. The claim language has now been amended to read "A nucleic acid construct", which applicants assert does not read on a human or a product of nature.
>
> These arguments are adopted in regards to the amended claims reading on a human, but it is maintained that the claims continue to read on a product of nature, since the instant claims read on a chromosome is undergoing replication and is therefore a product of nature. This is because a chromosome could be considered a primary nucleic acid, which acts as a template for the synthesis of a secondary nucleic acid (the daughter chromosome),

> which acts a template for the synthesis of a gene product which is could be a sense RNA. The rejection is maintained therefore.
>
> Claims 299, 303, 304, 308-313 and 317 were similarly rejected as reading on nonstatutory subject matter, i.e., both a human and a product of nature.
>
> Prior to the instantly submitted amendment, independent claim 299 recited "A nucleic acid which upon introduction into a eukaryotic cell produces more than one specific nucleic acid, each such specific nucleic acid produced being substantially nonhomologous with each other and being either complementary with the specific portion of one or more viral or cellular RNAs in a cell or binds to a specific viral or cellular protein."
>
> In response, applicants have amended the preamble to recite "a multi-cassette nucleic acid construct comprising either more than one promoter or when the initiator or both", and assert that this amendment is "certainly not a product of nature or human being."
>
> These arguments are adopted in regards to the amended claims reading on a human, but it is maintained that the claims continue to read on a product of nature. The claims read on a chromosome which is undergoing replication and is therefore a product of nature, because a chromosome can be considered a multi-cassette nucleic acid construct, which certainly comprises more than one promoter, which produces more than one specific nucleic acid, which are substantially nonhomologous with each other and are complementary to a specific portion of one or more cellular RNA targets, since a chromosome is double stranded and therefore comprises the antisense strand. The rejection is maintained therefore.

These rejections were discussed during the June 29, 2006 interview. Applicants maintained that "nucleic acid construct" does not occur in nature. However, as discussed during the June 29, 2006 interview, in order to advance prosecution, claim 245 has been amended to recite that the claimed composition comprises **an isolated** primary nucleic acid construct. Furthermore, claims 265 and 299 have been amended to be directed to "an isolated nucleic acid construct". Claims 248, 249, 251, 253-255 and 264 depend form claim 245 and claims 303-304, 308-313 and 317 depend from claim 299. Therefore, arguments made with respect

to claims 245 and 299 would apply to the dependent claims as well.

In view of the amendments of claims 245, 265, and 299, Applicants assert that the rejection of claims 245, 265 and 299 under 35 USC §101 have been overcome. Therefore, Applicants respectfully that the rejection under 35 USC §101 be withdrawn.

3. The Rejection Under 35 USC §102(b)

Claims 245, 248-251, 253-255, 260, and 264, are rejected under 35 U.S.C. 102(b) as being anticipated by Bebenek et al. (J. Biol. Chem. 1989. 264(28) 16948-16956) (hereinafter "Bebenek"), claims 265, 268, 270, 284, and 288-290, and 296 are rejected under 35 U.S.C. 102(b) as being anticipated by Izant, J et al. (Chimeric antisense RNAs. Raven Press Series on Molecular and Cellular Biology (1992), 1 (Gene Regul.), 183-95) (hereinafter "Izant") and claims 299 and 303, 304, and 308-313 are rejected under 35 U.S.C. 102(b) as being anticipated by Junker et al. (Antisense Res Dev. 1994 Fall; 4(3): 165-72.) (hereinafter "Junker"). Each of these rejections are addressed in detail below:

3.1 Bebenek

As noted above, claims 245, 248-251, 253-255, 260, and 264 have been rejected under 35 USC §102(b) over Bebenek. The Office Action specifically states

> .....These claims were rejected over Bebenek et al., who teach that HIV virions reproduce imperfectly, which result in an average of five mutations per genome per round of replication. Essentially, the fact that Bebenek indicates that an average of five mutations occurs per round of replication is considered to indicate that the final product is mutated compared to the primary nucleic acid, which satisfies the limitation that the primary nucleic acid is not obtained from the secondary nucleic acid or gene product. Accordingly, Bebenek et al. teaches a primary nucleic acid construct, i.e. the HIV virion, which gives rise to a secondary nucleic acid, which in turn gives rise to a sense nucleic acid, which is the virus containing an average of five mutations, and is therefore considered to be different

and thus not obtained from the primary nucleic acid construct. Clearly, since the sense nucleic acid contains promoter's terminators etc., it is also considered to comprise a signal sequence, thus meeting all the limitations of the above claimed invention.

Applicants dispute this by asserting that Bebenek et al. is not a study on in vivo HIV replication, and rather, occurs in an artificial system. Applicants point to the abstract statement of Bebenek "if operative in vivo' which applicants suggest casts doubt as to whether the "gene product" element of the claim would be any different from the primary nucleic acid when the construct is expressed in a cell, a situation which is expressly disclaimed in the recited invention.

This is not considered convincing, because A) the system of Bebenek et al. utilizes all the components utilized in the HIV replication process, indicating that such components would act identically in the cell, and B) there is no evidence that further suggests that the system would behave any differently inside a cell. In fact, the phrase "if operative in vivo" is offered by Bebenek as support merely for the rate of mutation, and does not cast doubt as to whether HIV mutates. This is because, as one of ordinary skill would understand, the rate of mutation is attributed exclusively to the fidelity of the polymerase enzyme, a property which is not affected by whether the enzyme if functioning a cell or not. At no point does Bebenek cast doubt on whether or not this process occurs in a cell, because it is well accepted that HIV mutates from its original form. Bebenek et al. merely says that if the rate they see in their assay operates in vivo at the same rate observed in the studies, then the average virion contains 5 mutations. The prima facie case of anticipation is satisfied with this teaching. It is applicants' responsibility to provide evidence or reasoning as to why a process that occurs in the presence of all critical cellular components would not otherwise occurs inside the cell, and mere assertions to the contrary will not take place of such evidence or reasoning.

Applicants also argue that the reported error rate of HIV reverse transcriptase of 5 mutations per genome would result in a situation where "it is likely that one would obtain some genomes with no mutation." Applicants argue that the mere fact that a certain thing may result from a given

> set of circumstances is insufficient to prove anticipation, and the rejection should be withdrawn accordingly.
>
> This is not considered convincing. Bebenek does not teach that mutations "may" occur. Bebenek et al. teaches that they *do* occur, at a rate of about 5 mutations per replication. While it may not be out of the realm of possibility to assert that HIV replication has occurred error-free at some point in time, this does not mitigate the fact that mutations have and do occur. Applicants have not provided any evidence or reasoning beyond mere assertion that refutes that Bebenek et al. teaches that mutations occur during HIV replication, and that such mutations are inherent to the process of HIV replication. The rejection is maintained therefore.

Applicants respectfully traverse the rejection. As discussed, during the interview on June 29, 2006, Applicants assert that mutations do not always occur in Bebenek. This is clearly evident on page 16949, col. 1, lines 3-24 where the calculation of the error rate is described. A portion of this passage is reproduced below for Examiner's reference.

> The mutation assay (citation omitted) was performed as described (citation omitted). In all cases, error rates for HIV-1 RT were calculated using a forward mutant frequency of 390 x 10-4, a minus-strand expression value of 0.6 (citation omitted), the date from the sequence analysis of mutants (Fig. 1 and the phenotypically detectable mutations in Table II), and the known number of detectable sites for the type of effort under consideration. As an example, the frameshift error rate shown in table I was calculated by dividing the frequency ((234/439) x (390 x 10-4)) of this class of errors by 0.6 (the probability of expressing a polymerase error in the newly synthesized minus strand) and then dividing by 150, the known number of sites at which frameshift errors can be detected.

It is clear that in Bebenek that while mutations do occur, they do not occur 100% of the time. Therefore, it would follow in Bebenek that a primary nucleic acid is sometimes obtained with the secondary nucleic acid or gene product. In contrast, it

is recited in claim 245 that the primary nucleic acid **is not** obtained with the secondary nucleic acid or the gene product.

Given that mutations do not always occur and thus a primary nucleic acid is sometimes obtained from a secondary nucleic acid, the criteria for inherency has been met. As stated in the MPEP 2112

> To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient'. *In re Robertson, 169 F.3e 743, 745, 49 USPQ2d 19490, 1050-1 (Fed. Cir. 1999)*

As discussed above, probability determinations are actually part of the formula in determining mutation rate. Furthermore, as noted above, mutations are not always present in the product obtained in the method of Bebenek.

Claims 248-251, 253-255, 260 and 264 depend from claim 245. Therefore, arguments made with respect to claim 245 apply to these dependent claims as well.

In view of the above arguments, Applicants assert that the rejection over Bebenek have been overcome. Therefore, Applicants respectfully request that the rejections be withdrawn.

3.2 Izant

Claims 265, 268, 270, 284, and 288-290, and 296 have been rejected under 35 U.S.C. 102(b) as being anticipated by Izant. The Office Action specifically asserts

> Claims of the instant invention are drawn to a nucleic acid construct which encodes a secondary nucleic acid which comprises a nuclear localization sequence comprising a portion of snRNA, which has at least two stem loops present at the 3' end of the native snRNA and also a reimportation signal, and an antisense. The antisense may consist of DNA, RNA, a DNA-RNA hybrid, a DNA-RNA chimera, and the combination of the foregoing, or wherein the nuclear localized sequence comprises a portion of UI RNA comprising C and D loops, as well as cells, biological systems, and methods of use thereof.

> Izant et al. teaches a nucleic acid construct which encodes a secondary nucleic acid which comprises a nuclear localization sequence comprising a portion of snRNA, which has at least two stem loops present at the 3' end of the native snRNA and also a reimportation signal, and an antisense. The antisense may consists of RNA, and the nuclear localized sequence comprises a portion of UI RNA comprising C and D loops. Izant et al. also teaches cells, biological systems, and methods of use thereof. See figure 1, for example.

Applicants respectfully traverse the rejection. However, in order to advance prosecution, claim 265 has been amended to recite that the construct comprises: (a) a nuclear localization sequence comprising a portion of snRNA comprising sequences for two loops and a reimporation signal and (b) (b) a reimportation signal and (ii) an antisense nucleic acid sequence, wherein said antisense nucleic acid sequence replaces sequences that participated in stem-loop formation in said snRNA.. As discussed during the interview on June 29, 2006, in contrast to the claimed construct, the antisense sequence in Izant **does not** replace sequences that participated in stem-loop formation in said snRNA.. To more clearly illustrate the differences between the subject matter recited in claim 265 and Izant, Applicants herewith submit as Exhibit 3 a copy of Figure 1 of Izant and Figure 41 of the instant application.

Claims 268, 270, 284, and 288-290, and 296 depend from claim 265. Therefore, arguments made with respect to claim 265 apply to these claims as well.

In view of the above arguments and the amendment of claim 265, Applicants assert that the rejection of claims 265, 268, 270, 284 and 288-290 under 35 USC §102(b) have been overcome. Therefore, Applicants respectfully request that the rejection be withdrawn.

3.3 Junker et al.

Claims 299 and 303, 304, and 308-313 are rejected under 35 U.S.C. 102(b) as being anticipated by Junker. The Office Action specifically asserts:

> The instant claims were rejected previously because Junker et al. discloses the use of a vector comprising sequences encoding two different antisense oligos targeted to HIV. Thus, Junker et al. teaches a nucleic acid which produces more than one specific nucleic acid which are nonhomologous with each other and are complementary to a specific portion of an RNA target.
>
> Applicants traverse the rejection by arguing that Junker et al. do not teach all the limitations of the instant claims because only one transcript is actually expressed. This is considered to be incorrect, particularly when taking into account the teachings of figures IA and 1C. Figure 1A teaches a sequence that encodes two distinct antisense sequences; the first is DCT5T-αtat, and the second is DCT5T-αrev. Figure 1C teaches that the two antisense sequences are separate. Thus, contrary to applicant's arguments, the construct of Junker et al. produces more than one specific nucleic acid transcript as required by the instant claims. Furthermore, the claim language requires "either more than one promoter or one initiator or both". While it is agreed that such language stipulates that more than one promoter is required, there is no such requirement that the modifier of "more than one" is also directed to "initiator".
>
> Thus, one interpretation is that there need be only one initiator, which is considered to be taught by Junker et al. Claims 310 and 311 are rejected because they limit embodiments not required in the claims (i.e. they limit recitations recited in the alternative in the independent claim, and thus not required in the dependent claims).

Applicants respectfully traverse the rejection. This particular rejection was discussed during the June 29, 2006 interview. As discussed, claim 299 has been amended to recite that the multi-cassette construct comprises either more than one promoter and/or more than one initiator thereby allowing the expression of more than one individual transcript. In contrast, the construct in Junker contains two copies of a single antisense module, one at the 5' end and a second identical copy at the 3' end. As was discussed at the interview, the text of the Junker paper may have been ambiguous since they were discussing the properties of two separate modules, one for expression of anti-tat and a second for anti-rev. However, these were meant to be alternatives, not as a combination.

As discussed during the June 29, 2006 interview, Applicants submit herewith as Exhibit 4, Sullenger et al., 1990, Mol. Cell. Biol. 10: 6512-6523 (hereinafter "Sullenger"). Sullenger is referenced in Junker when the vector is being described. Figure 1 of Sullenger shows that a single insertion of a tRNA expression cassette in the 3' LTR region results in a construct with a copy at the 5' end also being created after entry into the target cell. This is strictly a consequence of the replication pathway of a retroviral vector. Consequently, it can be seen in the abstract of Sullenger that this type of vector system was referred to as a "double copy" vector. Furthermore, Applicants also herewith submit as Exhibit 5 for Examiner's reference a copy of Junker et al., 1995, Gene Therapy 2:639-646 (hereinafter "Junker 1995"). This reference was published after the cited Junker reference but is obviously from the same research group. In order to put these references on the record, Applicants herewith submit a PTO 1449 form and Supplemental Information Disclosure Statement listing these references.

In Figure 1 of Junker 1995, the structure of the vector used to express the tRNA-antisense fusion transcript (DCT5T-αrev) shown in Figure 1B of the Junker reference cited in the instant Office Action is clearly depicted as existing as a single copy in the 3' end of the plasmid construct and having a copy at each end in the proviral form, integrated into the target cell's chromosomal DNA. It should be pointed out that a consequence of this design is that even if a plasmid was designed that used the same site in the 5' end for a second cassette as was used in the 3' end, this would be a useless exercise since this information would be lost during the replicative cycle and only two copies of the 3' end cassette would be present in the provirus. As noted above, it is clearly evident that the construct in the cited Junker reference only produces two identical copies of the same antisense.

Applicants in response to the issue raised with respect to claims 310 and 311 note that claim 324 has been added to depend from claim 299 and recite that said specific nucleic acid sequence binds to a specific cellular protein. Claims 310 and 311 now depend from claim 324. Claims 310 and 311 now recite embodiments now required in the dependent claims.

In view of the above arguments and the amendment of claims 299, 310 and 311, Applicants assert that the rejections of claims 299 over Junker et al. under 35 USC §102(b) has been overcome. Therefore, Applicants respectfully request that the rejection be withdrawn.

SUMMARY AND CONCLUSIONS

It is Applicants belief that the pending claims are in condition for allowance. However, if a telephone conversation would further the prosecution of the present application, Applicants' undersigned attorney request that he be contacted at the number provided below.

Respectfully submitted,

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Dated: 12/20/06

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